REMARKS

Preliminary Remarks

Claims 107-111 and 117-132 are under active examination. Claims 112-116 and 117-121 are canceled with this response. Claims 122, 124, 125 and 127-129 are proposed to be amended to alter dependency. Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application. No new matter is added by the proposed amendments.

The Notice of Non-Compliant Amendment, mailed March 5, 2010, asserted that Applicants' amendments, filed January 27, 2010, are not in compliance with 37 CFR 1.121 because claims 112-116 are listed as being "withdrawn" when they have been "canceled". Applicants have scoured the record of the present application and cannot find any evidence that claims 112-116 were canceled.

Claims 112-116 were added by an amendment filed January 31, 2002. The Examiner subsequently issued an Office action, dated April 26, 2002 requiring restriction of the claimed subject matter to one of four groups of inventions set forth by the Examiner. In response, Applicants filed a reply dated May 20, 2002 electing Group III (claims 89 and 102-111) for further prosecution. The Examiner then issued an Office action, dated August 8, 2002 indicating under the "Disposition of the Claims" heading that claims 112-116 were withdrawn from consideration and also explicitly stating that these claims were withdrawn at page 2 ("Claims 90-101 and 112-116 have been withdrawn from consideration"). The subsequent Office action, dated April 28, 2003, also indicated that claims 112-116 were withdrawn from consideration. Moreover, the listing of claims in Applicants' reply filed June 26, 2006 indicated that claims 112-116 were withdrawn from consideration and every subsequent reply filed by Applicants in which amendments to the claims were presented, lists the status of claims 112-116 as withdrawn from consideration. Applicants cannot find any evidence on the record that claims 112-116 were ever canceled. Accordingly, Applicants believe that their reply, filed January 27, 2010 is fully compliant with 37 CFR 1.121.

Nonetheless, in the interest of clarifying the record of the present application, Applicants now explicitly cancel claims 112-116 and identify the status of these claims as such. Applicants

believe that this Amendment is fully compliant with 37 C.F.R. 1.121 and therefore respectfully request entry of the Amendment.

A. The Rejections of Claims 107-111 and 117-132 Under 35 U.S.C. §§ 103(a) Should Be Withdrawn

Claims 107-111 and 117-132 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bram *et al.* (WO 98/39361) (hereinafter "Bram PCT") in view of Presta et al. (U.S. Patent No. 5,739,277) (hereinafter "Presta") for "reasons of record."

Claims 107-111 and 117-132 also stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bram *et al.* (US Patent No. 5,969,102) (hereinafter "Bram US") in view of Presta for "reasons of record."

Claims 117-121, directed to the use of a fusion protein that binds ztnf4 consisting of amino acid residues 1 to 154 of SEQ ID NO: 6 joined by a peptide bond to an immunoglobulin heavy chain constant region, are proposed to be canceled with this response. The remaining claims are directed to the use of a fusion protein that binds ztnf4 consisting of amino acid residues 25-104 of SEQ ID NO: 6 joined by a peptide bond to an immunoglobulin heavy chain constant region. With respect to these claims, Applicants respectfully request reconsideration and withdrawal of the rejections in view of the following arguments.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the Examiner must provide a clear articulation of the reasons why the claimed invention would have been obvious, i.e., the Examiner must provide a reason one of ordinary skill in the art would have combined the cited references to arrive at the claimed invention. Second, there must be a reasonable expectation of success. That is, the hypothetical person of ordinary skill in the art, at the time the invention was made, must have had a reasonable expectation that the proposed modification or combination would work to produce beneficial results. *See* MPEP § 2143.02. Finally, "to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981 (CCPA 1974). The burden of establishing a *prima facie* case of obviousness lies with the Examiner, and the expectation of success must be found in the prior art, not the applicant's disclosure. *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir. 1988)

i. Bram (PCT and US) Fails to Teach or Suggest the Presently Claimed Fusion Proteins

Applicants respectfully submit that the Examiner has failed to make the underlying factual findings necessary to establish a *prima facie* case of unpatentability. In particular, the Examiner has failed to clearly articulate how one of ordinary skill in the art would arrive at the presently claimed TACI fragment based on the cited references. Bram (PCT and US) provides a general disclosure and partial characterization of the TACI protein. Although brief reference is generically made to TACI fragments and TACI fusion proteins, with respect to the TACI extracellular domain only a single fragment consisting of the entire ~ 166 amino acid extracellular domain is specifically disclosed and only a single fusion protein consisting of the ~ 166 amino acid extracellular domain fused to another peptide is disclosed. There is no disclosure of *any* sub-fragment of the TACI extracellular domain (or fusion protein containing same), much less the specifically claimed fragment consisting of amino acids 25-104 of SEQ ID NO: 6. The presently claimed fragment, *corresponding to less than one-half the length of the TACI extracellular domain*, is simply not taught by Bram, nor does Bram provide any suggestion that could lead one of ordinary skill in the art to remove 24 and 62 amino acids from the N- and C-termini of the TACI extracellular domain, respectively. Therefore Bram cannot provide motivation to the skilled artisan to make fusion proteins containing the specifically claimed fragment. The Examiner's position appears to be that because methods for making protein fragments were known, it would have been obvious to one of ordinary skill in the art to make all possible TACI fragments until, by chance, the presently claimed fragment was produced. In other words, the Examiner bases his finding that the present claims are unpatentable on an "obvious to try" analysis. As discussed below, such an analysis is not proper in the present case.

a. Relevant Case Law

The U.S. Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007), found that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of **identified, predictable solutions**, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." (emphasis added). *Id.* at 1732. Thus, according to the Court, in certain limited situations, a *prima facie* case of obviousness may be predicated on an 'obvious to try' analysis. However,

such an analysis is not proper unless: (1) the solutions are identified, small in number and easily traversed in the context of the art and (2) there is a reasonable expectation of success.

The Federal Circuit recently clarified the situations in which an 'obvious to try' analysis may be used to find patent claims obvious. In *Ortho-McNeil Pharmaceutical v. Mylan Labs*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), the Federal Circuit held that patent claims to a pharmaceutical were not obvious in view of the standard set forth in *KSR*. In reaching its decision, the Court found that, although a key ingredient of the invention may have been one of many a skilled artisan might have tried, evidence showed it was "not the easily traversed, small and finite number of alternatives that KSR suggested might support an inference of obviousness." Moreover, the court referenced the need to avoid "hindsight", stating that the inventor's "pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted." *Id.* The Court also emphasized that "a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis such as occurred in this case." *Id.*

In *In re Kubin*, 90 U.S.P.Q.2d 1417, 561 F.3d 1351 (Fed. Cir. 2009), the Federal Circuit set forth factual situations where an obvious to try analysis may not be applied. In particular, "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness (emphasis added)." *Id* at 1423. According to the Court, such cases are the inverse of the proposition set forth in *KSR* that obviousness may arise where a skilled artisan merely pursues "known options" from a "finite number of identified, predictable solutions," *Id.* In *Kubin*, the prior art disclosed a protein, a monoclonal antibody to the protein, and a routine method by which the DNA encoding the protein could be cloned. The Court found that an obvious to try analysis was proper because practicing the exact method disclosed in the prior art inevitably led to the precise DNA sequence discovered by the inventor. Because this was not a case where the skilled person was faced with combinatorial prior art possibilities, the Court found the obvious to try analysis to be proper and affirmed the lower court's decision that claims covering the encoding DNA were obvious.

b. Analysis

The Examiner acknowledges that Bram PCT and Bram US each fails to disclose (i.e. **identify**) any particular sub-fragment of the TACI extracellular domain, much less the presently

claimed sub-fragment consisting of amino acid residues 25-104 of SEQ ID NO: 6. Nonetheless, according to the Examiner, it would have been obvious to the skilled artisan to produce the specifically claimed fragment of the extracellular domain and test it for observed biological activity. In other words, The Examiner argues that because methods for making protein fragments were known, that it would have been obvious to one of ordinary skill in the art to make all possible TACI fragments and test them for the ability to bind a then-unidentified ligand until, by chance, the presently claimed fragment was produced.

Such an analysis is contrary to the U.S. Supreme Court and Federal Circuit precedent discussed above. Indeed, the facts of the present case fit squarely within the class of cases for which *Kubin* forbids such an analysis. As discussed in Applicants' prior response, for a polypeptide of a given length, there is an inverse relationship between the number of potential fragments that can be constructed and the size of a given fragment. For a polypeptide of 166 amino acids (corresponding to the TACI extracellular domain disclosed by Bram PCT and Bram US), there are 157 ten-amino acid fragments, 156 eleven-amino acid fragments, 155 twelve-amino acid fragments and so forth. Excluding fragments below 10 amino acids, there are total of (157 + 156 + 155....+ 3 + 2) or 12,402 fragments. Such is not a small or easily traversed number. Even if one were to consider only fragments having 80 amino acids (corresponding in size to the claimed fragment consisting of amino acid residues 25-104), there are 87 possible 80-amino acid fragments of the TACI extracellular domain. In any event, the genus of potential fragments is vast and the prior art of record provides no guidance which could lead the skilled artisan to remove 24 and 62 amino acids from the N- and C-termini of the TACI extracellular domain, respectively, to obtain the specifically claimed fragment. This is not a case where a skilled artisan could merely pursue "known options" from a "finite number of identified, predictable solutions" nor can the vast genus of potential fragments be considered small and/or easily traversed.

Moreover, the skilled artisan would have to test each of the vast number of possible TACI extracellular domain sub-fragments for the ability to bind ztnf4, because Bram PCT and Bram US make only a general statement that the ligand binding domain is located *somewhere within the TACI extracellular domain*. Neither Bram PCT nor Bram US identify a TACI ligand which could be used to identify which, if any, of the over twelve-thousand extracellular domain fragments retain ligand-binding capability. Thus, there is simply no way to predict from Bram

PCT or Bram US which if any of the vast number of possible TACI extracellular fragments would constitute ligand-binding fragments. In this regard, the Examiner's attention is directed to Applicants' prior response, in which evidence was filed demonstrating that, at the time of the present invention, it was unpredictable whether protein fragments comprising an extracellular ligand binding domain would retain ligand-binding function. Predictability that the presently claimed fragment, which is missing 24 and 62 amino acids from the N- and C-termini respectively, would retain ligand-binding capability is substantially further decreased. Because Bram (PCT and US) fails to identify any ligand-binding fragment of the TACI extracellular domain or provide any guidance which could lead the skilled artisan to the specifically claimed fragment, the skilled artisan would have had to "throw metaphorical darts at a board filled with combinatorial prior art possibilities" in order to arrive at the presently claimed subject matter. Therefore, according to *Kubin*, the Examiner has failed to establish that the claimed subject matter is obvious.

The Examiner, at page 4 of the Office Action, states that *KSR* is the controlling case law with regard to 'obviousness'. However, the Examiner's analysis is improper in view of *KSR*, which limits application of the obvious to try analysis to cases where the prior art discloses a finite number of **identified, predictable solutions**. As discussed above, Bram US and PCT fail to **identify** any TACI extracellular sub-fragment and there is simply no way to **predict** from Bram PCT or Bram US which if any of the vast number of possible TACI extracellular fragments would constitute ligand-binding fragments.

The Examiner also attempts to distinguish the fact pattern in *Ortho-McNeil* from the present case. However, Applicants cited *Ortho-McNeil* for the guidance provided by Federal Circuit to those applying the principles set forth in *KSR*, which guidance is not limited to the fact pattern of that case. As acknowledged by the Examiner, the Federal Circuit in *Ortho-McNeil* warned that the "obvious to try" analysis discussed in *KSR* is only properly applied in situations with a finite and in the context of the art, small and/or easily traversed number of options. If it is the Examiner's contention that court decisions are only applicable to cases with identical fact patterns, then *KSR* would seem to be inapposite to the present case as well, as it dealt with gas pedal technology and not fusion proteins for medical use. At any rate, as discussed above, the number of possible fragments of the TACI extracellular domain is over **12,000**, which one of ordinary skill in the art would not consider to be a small **or** easily traversed number as alleged by

the Examiner, particularly in view of the fact that TACI ligands were unknown at the priority date of the present application.

The disclosure of Presta does nothing to rectify the aforementioned failure of Bram PCT and Bram US to disclose the specifically claimed fragments.

Based on the aforementioned, it is clear that the Examiner has failed to make the requisite underlying factual findings as to how one of ordinary skill in the art could have arrived at the specifically claimed TACI fragment consisting of amino acids 25-104 of SEQ ID NO: 6, and has improperly applied an "obvious to try" standard in finding the claims obvious over the cited prior art. Here, the prior art teaches generally that the ligand binding portion of TACI is located somewhere on the extracellular domain. The Examiner's contention that it would have been obvious to make and screen the multitude of fragments representing all possible overlapping peptides derived from the protein in order to find the specifically claimed ligand binding fragment is directly analogous to throwing "metaphorical darts at a board filled with combinatorial prior art possibilities" which, according to the Federal Circuit's decision in *Kubin* cannot serve as the basis for finding claims 107-111 and 117-132 obvious. In this respect, it is clear that the Examiner has impermissibly used hindsight reconstruction to retrace the path of the present inventors and discounted the number of possible TACI extracellular domain sub-fragments. Thus, the pending claims are, as a matter of law, nonobvious over each of Bram PCT and Bram US in view Presta under 35 U.S.C. § 103(a) and the Applicants respectfully request withdrawal of the rejections.

ii. Bram (PCT and US) Fails to Provide a Reasonable Expectation of Success

Applicants also respectfully submit that Bram PCT and Bram US each fails to provide a reasonable expectation of success in achieving the presently claimed methods. Whether the prior art provides a reasonable expectation of success is made at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986). Moreover, to "to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 165 (Fed. Cir. 2006). Finally, a reasonable expectation of success requires more than where the prior art teaches merely to pursue a "general approach that seemed to be a promising

field of experimentation" or "gave only general guidance as to the particular from of the claimed invention or how to achieve it." *Medichem*, 437 F.3d at 1167. Applicants respectfully submit that Bram PCT and Bram US each fails to provide any guidance that could lead one of ordinary skill in the art to reasonably expect that administration of the claimed fusion protein would be effective in inhibiting B lymphocyte proliferation.

While obviousness does not require absolute predictability, at least some degree of predictability is required. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). As a corollary to this "predictability" requirement, the Federal Circuit, as recently as August 5, 2009, emphasized that:

> [The *O'Farrell* decision] observed that most inventions that are obvious are also obvious to try, but found two classes where that rule of thumb did not obtain.
>
> First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *O'Farrell*, 853 F.2d at 903. This another way to express the *KSR* prong requiring the field of search to be among a "finite number of identified" solutions. 550 U.S. at 421; *see also Procter & Gamble*, 566 F.3d at 996; *Kubin*, 561 F.3d at 1359. It is also consistent with our interpretation that *KSR* requires the number of options to be "small or easily traversed." *Ortho-McNeil Pharm. Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). *Bayer Schering Pharma AG v. Barr Laboratories Inc.*, 91 USPQ2d 1569, 1572-73 (Fed. Cir. 2009).

Turning to the facts in the instant prosecution, the Examiner alleges that "the number of possible deletion mutants encompassed by the instant claims is not only finite but easily

traversed," and that the functionality of fusion proteins comprising such fragments "can easily be determined via B cell activation." However, the Examiner has not pointed to any guidance in Bram PCT or Bram US as to particular sub-fragments that would be likely to retain this ability. In the absence of such guidance, and in view of the unpredictability inherent in this art, one of ordinary skill in the art lacks a reasonable expectation of success that the presently claimed fragment, which is missing 24 and 62 amino acids from the N- and C-termini of the TACI extracellular domain respectively, would bind ztnf4 and inhibit B lymphocyte proliferation.

Contrary to the Examiner's assertion, one of ordinary skill in the art must resort to undue experimentation in order to arrive at the presently claimed fragment based on the disclosure of Bram. In order to arrive at the presently claimed invention, one of ordinary skill in the art must create literally *thousands* of fragments of the TACI extracellular domain, and test each fragment for the ability to inhibit B cell proliferation without the benefit of knowing the identity of any TACI ligand. Indeed, it is undisputed that Bram does not disclose any TACI ligand. Moreover, Bram (PCT and US) does not provide any working example demonstrating efficacy *in vivo* of any fusion protein containing any TACI fragment. Only through the present disclosure is one of ordinary skill taught the identity of ztnf4 as a ligand for the TACI receptor and the use of fusion proteins containing the presently claimed ztnf-binding sub-fragment of the TACI extracellular domain. Applicants respectfully submit that the Examiner's conclusion of obviousness amounts to impermissible hindsight reconstruction based on information gleaned from the present disclosure.

Presta, while teaching the fusion of the Fc fragment with other proteins to increase the circulating half-life, fails to remedy the aforementioned infirmities of Bram PCT and Bram US.

As discussed above, Bram PCT and Bram US each provides only a general approach to a promising field of experimentation and provides nothing more than general guidance as to how to achieve the presently claimed invention. Accordingly, for at least this reason, Bram PCT and Bram US each fails to render the subject matter of the present claims obvious. Withdrawal of the rejections of claims 107-111 and 117-132 under 35 U.S.C. § 103(a) is thus requested.

B. <u>The Rejections for Obviousness-type Double Patenting</u>

Claims 107-109, 117-119 and 122-123 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-4 of

copending Application No. 11/748,978. Claims 107-109 and 117-119 are newly rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 84-86 of copending Application No. 09/569,245. Applicants wish to defer the response to these provisional rejections until the claims are otherwise allowable.

Conclusion

In view of the above remarks, applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at (312) 595-1408. Should any additional fees be deemed necessary in connection with the filing of this document, the Commissioner is hereby authorized to deduct any such fees from Deposit Account No. 08-3038 referencing the above attorney docket number.

Respectfully submitted,
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